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HETEROTRANSPLANTATION OF A HUMAN MALIGNANT TUMOUR TO "NUDE" MICE

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Many attempts have been made to transplant human malignant tumours to various laboratory animals. As a general rule, the outcome of such attempts will be negative, due to immune reactions.

Changes in immune responsiveness may alter this result. Thus, neonatal thymectomy has been shown to increase survival of xenogeneic tumours (1). This report concerns serial transplantation of a human adenocarcinoma to the mouse mutant "Nude", suffering from recessive thymic aplasia (2, 3).

Materials and Methods

Eight-week-old mice of the mutant "Nude", bred in Patologisk Anatomisk Institut, Kommunehospitalet, Copenhagen (3), were employed. Controls were phenotypically normal littermates, presenting a normal fur. These controls were inoculated to exclude a loss of antigenicity in the primary tumour. Out of 4 malignant tumours tested (two anaplastic mammary carcinomas and two carcinomas of the colon) one has shown take.

The tumour used was taken from a 74-year-old woman (No. 20,246/69, Surgical Department I, Kommunehospitalet). The patient underwent abdominal surgery for a tumour of the sigmoid colon. During the operation several big metastases of the liver were noticed. The operative specimen was 16 cm in lenght and had a 3 cm broad circular tumour growing through all the layers of the sigmoid colon. Microscopy (No. 6792/69) showed a rather highly differentiated mucoid-producing adenocarcinoma with total penetration of the wall. 15 minutes after removal, a cube of tissue measuring 5 × 5 × 5 mm was excised from the serosal side of the tumour under sterile precautions. The cube was minced with a pair of scissors in 5 ml of Tissue Culture Medium "199" (Glaxo). Using a 12 G canula, 0.5 ml of the suspension obtained was injected subcutaneously in the lateral abdominal wall in 3 Nudes and 3 controls.

On the 21st day after inoculation parts of the two biggest tumours developed were removed for microscopical examination and serial transplantation. A small block of this tumour tissue (2 × 2 × 2 mm) was implanted subcutaneously in the lateral abdominal wall in 6 Nudes and 1 control.

After 14 days biopsies were taken from two of the Nudes of transfer No. 2.

Specimens for microscopical examination were fixed in formalin, paraffin-embedded and stained with hematoxylin-eosin and van Gieson-Hansen stain.

Results

After 6 days a recognizable tumour appeared at the inoculation site in all the animals. Whereas the tumours regressed slowly in the controls, there was a rapid increase in the size of the tumours in the Nudes. On the 40th day after inoculation tumour masses measured 10 × 20 × 25 mm in two of the mice and 5 × 5 × 12 mm in the third mouse of the first transfer. In the controls no palpable tumour masses could be detected. Microscopical examination showed no tumour growth.

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Fig. 1.

Top: Section from operative specimen (KH 6792/69).
Bottom: Biopsy from transfer No. 1 after 21 days. (Hematoxylin-eosin, 140 ×).

The pattern of growth in transfer No. 2 was the same as in the first inoculation. Tumour growth thus appeared in all inoculated Nudes. In no case palpable metastases were found, and no ascites developed. The animals have been kept alive for further investigations.

The macroscopical appearance was that of a rather well circumscribed, finely nodular, solid tumour. The cut surface as seen during biopsy was light grey and glary. Histologically the tumour has remained constant during the transfers and has the characteristics of the primary tumour as to degree of differentiation, contents of connective tissue stroma, and production of mucoid material.

Discussion and Conclusions

Earlier attempts at heterotransplantation of tumours have shown that a successful outcome depends on transplantation to an immunologically unresponsive location in a normal animal, *e.g.* the hamster cheek pouch or the anterior eye chamber in various species, or transplantation to an immunologically unresponsive animal, *e.g.* after exposure to X-ray irradiation, cortisone treatment, induction of immunological tolerance, or neonatal thymectomy. The Nude represents an analogue to the latter condition, only that thymic aplasia would exclude any prenatal effect of the thymus on the organism. Nor is there any risk of neonatal thymectomy being subtotal.

The demonstrated serial growth of a human malignant tumour in the mouse mutant "Nude" is interesting mainly for two reasons:

a) It confirms the concept of the immunological deficiency of this mutant and
b) it may provide useful tools for the study of tumour immunity and for evaluation of therapeutic agents.

Summary

Serial growth of a human malignant tumour in a mouse mutant ("Nude") is reported for the first time.

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